Attorney Docket No.: RTS-0325
Inventors: Bennett and Wyatt
Serial No.: 10/016,149
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**REMARKS**

Claims 1, 2 and 4-18 are pending in the instant application. Claims 1, 2 and 4-18 have been rejected. Claims 11 and 16-18 have been canceled. Claims 1 and 15 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

**I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph**

Claims 15-18 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for antisense-mediated inhibition of phospholipase A2 Group V expression *in vitro* does not reasonably provide enablement for *in vivo* uses or methods of treating diseases; the Examiner cites several articles to support this position. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner=s suggestion that the cited references support the position that application of antisense *in vivo* is highly unpredictable or problematic.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable and that predicting efficacy based on *in vitro* data is problematic. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in humans. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals, and then to testing in humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity in humans.

The paper by Braasch and Corey (2002) describes the advances that have been made in the design of antisense compounds over the years. Included in the discussion are the types of advances that

are taught in the specification as filed. In fact, the paper states in the abstract that success in clinical trials with these agents has occurred. The Examiner, however, attempts to use this reference to emphasize that many obstacles persist in the art. This is not a proper use of this reference under 35 U.S.C. 112, first paragraph, as the teachings of a reference must be read in their entirety, not only in bits and pieces to support the Examiner=s interpretation. See MPEP 2141.02. A prior art reference must be considered in its entirety, *i.e.* as a whole, including portions that would lead away from the claimed invention. *W. L. Gore & Assocs., Inc. v. Garlock., Inc.*, 721 F. 2d 1540, 220 USPQ 303(Fed. Cir. 1983, *cert. denied*, 469 U.S. 851 (1984). This reference cites past problems and describes the advances that have been made in the design of antisense compounds over the years, including the types of advances that are taught in the specification as filed, so that antisense provides new potential both for research and clinical application. The authors conclude that:

> *Oligomers with improved chemical properties, combined with advances in cell biology and success in clinical trials,*

*are affording powerful new options for basic research, biotechnology and medicine (p. 4503, Abstract).*

Nothing in the Braasch reference teaches that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment; in fact at page 4504, Braasch teaches (referring to references 8 and 14-16) that those skilled in the art know how to deliver antisense oligonucleotides into various organs of both humans and animals (see, Braasch at 4504, column 2, *Uptake by Cultured Cells and Tissue Distribution in Animals*). Braasch teaches that use of transfection agents is routine in most types of cultured cells, but in contrast, uncomplexed phosphorothioate oligonucleotides spontaneously enter a number of tissues, including liver, kidney, spleen, intestine and other organs, when introduced intravenously (citing reference 8), and that *(p)romising data from ongoing clinical studies also suggest that oligomers can enter human tumors upon intravenous administration and produce a therapeutic effect* (references 8, 14-16).

As for teachings regarding toxicity and immunological problems, the Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of

drugs to marketed in the United States. (MPEP 2107.01) These possible side effects are not relevant to patentability. Nor are artifacts that may have obscured the intended antisense mechanism in certain situations, for which the Examiner cites Braasch. Braasch cites reference 3 (Stein) on this point; Stein teaches ways known in the art for avoiding nonspecific results, such as the importance of controls such as are taught in the instant specification.

Thus nothing in Braasch teaches or suggests that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment, nor does it teach that antisense compounds are inherently unpredictable when it comes to predicting *in vivo* activity based on well-designed *in vitro* studies.

Branch (1998) is also cited by the Examiner in support of his position. This paper teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects in humans is unpredictable. The Examiner, however, attempts to use this paper to support suggestions concerning the inaccessibility of most potential target RNA binding sites to antisense molecules and the unpredictability of antisense effects. One of skill in the art

would not expect to predict the "winning" antisense compound *a priori*, but would screen a reasonable number of compounds in order to find the one best suited to his or her needs. Time and difficulty of experiments are not determinative of enablement if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.(MPEP 2164.06). The fact that effective antisense drugs are selected from large pools of candidates and then optimized, rather than predicted *a priori*, does not indicate lack of enablement, *i.e.*, the need for undue experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Furthermore, the need to select an antisense compound from a pool of candidates is not unique to antisense drugs; all drugs are selected from large pools of candidates. While Braasch teaches

that the limited number of freely accessible RNA regions means that it may be necessary to screen 20 or more oligomers before finding one that functions adequately, in fact this 1-in-20 likelihood of success is high when compared to the odds of finding a traditional small molecule drug. Only five in 5,000 compounds make it from early research and preclinical testing to clinical trials, and of those five that enter clinical trials only one is approved (data from PhRMA, Pharmaceutical Research and Manufacturers of America).

The Office Action also cites Branch as supporting the unpredictability of non-antisense effects. The predictability, or lack thereof, of an effect which is not the claimed invention is irrelevant. One of ordinary skill is well aware of how to use proper controls to elucidate antisense inhibition of a desired target. Branch is also cited as teaching the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available (Page 46, second column). However, as discussed *supra*, the teachings of a reference must be read in its entirety, not only in bits and pieces to support the Examiner=s interpretation. See MPEP 2141.02. The full excerpt which has been cited in part by the Examiner begins, "As is true of all pharmaceuticals, the value of

a potential antisense drug"... In other words, antisense drugs are no different from any other drugs. If the need for evaluation of dose-response and therapeutic index were a bar to patentability, no drug would be patentable. Clearly this is not the proper standard. Thus nowhere does the reference of Branch teach that one of skill would be unable to use the compounds or methods of the invention in an *in vivo* environment.

The paper by Tamm et al. (2001) is another more recent review of the antisense technology and its specific application to oncology. Again, although the use of antisense is discussed in terms of what can go wrong, the paper, again, describes advances such as those taught in the instant specification. Nowhere do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity in humans. However, the Examiner cites this paper by Tamm concerning the undesirability of immunostimulation as a side effect and the unpredictability of this side effect, which, as discussed above, is irrelevant to the patentability of the claimed invention. Furthermore, Tamm teaches that the immunostimulatory activity can be ascertained experimentally, and can be avoided by several means.

The Examiner also cites Tamm as concluding that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach." The Examiner appears to be requiring Applicants to demonstrate that antisense is better than other drug development strategies. This is not required for patentability. The teaching in Tamm (that most other drug development strategies rely on an empirical approach) is supportive of the comparability of antisense to other drug development strategies, and thus to the ability of one skilled in the art to rely on Applicants' teachings, together with the knowledge of one of ordinary skill, to practice Applicants= invention.

As discussed for each of these references cited by the Examiner, the teachings of a reference must be read in its entirety, not only in bits and pieces to support the Examiner's interpretation. See MPEP 2141.02. Tamm, in fact, when taken as a whole, has a positive tone regarding the feasibility of the antisense approach in the clinic. "The specificity of this mechanism has resulted in a new class of drugs with a wide range of potential clinical applications. One approved antisense drug, and

results of several clinical antisense drug trials, show the feasibility of this approach, with some evidence for clinical efficiency." (Tamm, p. 489, column 2).

Two of the other references cited by the Examiner, Gars et al. (1996) and Agrawal (1996), likewise provide no basis to conclude that extrapolation from *in vitro* data to effects in humans is unpredictable or especially problematic.

The Examiner suggests that Gars teaches that the inhibitory activity of an oligonucleotide depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. Again, one of skill in the art would not need to predict an active antisense compound *a priori*, but would screen a reasonable number of compounds in order to find the one with inhibitory activity best suited to his or her needs. Such screening is taught in the instant specification and is routine for those in the art. Thus there is no need to predict the activity of an antisense compound when, as for other types of drugs, it can routinely be determined without undue experimentation. Nowhere does Gars teach that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment.

The Examiner suggests that the paper by Agrawal teaches difficulties in uptake of oligonucleotides by cells, and in particular that it is "difficult to generalize that all oligonuclectides are taken up in all cells with the same efficiency" (page 378) and that microinjection or lipid carriers may not be relevant for *in vivo* situations (page 379). As is well known in the art, there are many factors (discussed in Agrawal and elsewhere) that determine antisense efficacy and cellular uptake. There is, however, no requirement that all oligonucleotides (or all drugs of any class) behave identically.

As for the relevance of lipid carriers or microinjection for *in vivo* situations, the fact that these methodologies are irrelevant is not the same as a teaching that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment. In fact, as taught by Braasch and discussed above, uncomplexed (*i.e.*, without lipid carriers) oligonucleotides have been demonstrated to enter a number of tissues, including liver, kidney, spleen, intestine and other organs, when introduced intravenously, and clinical results suggest that oligomers can enter human tumors upon intravenous administration and produce a therapeutic effect. Thus nowhere does Agrawal teach that one of

skill would not be able to use the compounds or methods of the invention in an *in vivo* environment.

Further, the Examiner has failed to support the proposition that administration of antisense to phospholipase A2 Group V would be unpredictable based on any objective evidence. In contrast, data are provided in Example 15 showing the selection and design of antisense oligonucleotides to selected targets and their activity *in vitro*. Therefore, Applicants have clearly met their burden under 112, first paragraph. Further, Applicants respectfully remind the Examiner that the "absence of working examples should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement and the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation". In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). (MPEP 2164.02).

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 and canceled claims 16-18. Accordingly, withdrawal of this rejection is respectfully requested.

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**II. Rejection of Claims Under 35 U.S.C. 102**

Claims 1, 2 and 11 have been rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Tischfield et al. (US Patent 5,972,677). The Examiner suggests that this patent discloses three sequences (SEQ ID NO=s 15, 16 and 18) that possess 100%, 100% and 96.3% identity with residues 294-315, 522-543, and 526-552 of SEQ ID NO: 3 of the instant invention. The Examiner suggests that although this reference does not specifically teach inhibition of SEQ ID NO: 3 using these sequences, absent evidence to the contrary they are considered to possess the function due to their similarity to the claimed compounds. Applicants respectfully traverse this rejection.

At the outset, the claims have been amended to recite that the antisense compounds of the instant invention are targeted to a specific region within the sequence of phospholipase A2 group V of SEQ ID NO: 3, a region other than the regions listed by the Examiner. Support for this amendment to the claims can be found throughout the specification as filed but in particular at pages 80-83, Table 1.

Tischfield et al. disclose mammalian phospholipase A2 nucleotide sequences and antisense sequences. Although the patent discloses several sequences that overlap with residues within SEQ

ID NO: 3, nowhere does this patent teach or suggest antisense targeted to the specific region of human phospholipase A2 group V of SEQ ID NO: 3 as now claimed. In order to anticipate a claim the reference cited must teach each and every limitation of the claim (MPEP 2131). Therefore, this reference cannot anticipate the claims as amended and withdrawal of this rejection is respectfully requested.

Claims 1, 2 and 11 have been rejected under 35 U.S.C. 102(a) and 103(a) as being anticipated and/or obvious by Chen et al. (2001). The Examiner suggests that the reverse primer of human STS sts-stSG1697 of this reference possesses 100% identity with residues 966-989 of instant SEQ ID NO: 3. Applicants respectfully traverse this rejection.

Chen et al. (2001) disclose a mapping method for rapid assembly and ordering of bacterial artificial chromosome clones using sequence-tagged sites (STSs) and PCR. The 24 mer reverse primer referenced by the Examiner does overlap with some residues within SEQ ID NO: 3. However, nowhere does this paper teach or suggest antisense targeted to the specific region of human phospholipase A2 group V of SEQ ID NO: 3 as now claimed. In order to anticipate a claim the reference cited must teach each and every

limitation of the claim (MPEP 2131). Therefore, this reference cannot anticipate the claims as amended and withdrawal of this rejection is respectfully requested.

Claims 1, 2 and 11-14 have been rejected under 35 U.S.C. 102(e) and 103(a) as being anticipated and/or obvious by Shimkets et al. (WO 01/47944 A2). The Examiner suggests that this patent application discloses SEQ ID NO: 5308 which possesses 100% identity with residues 918-967 of instant SEQ ID NO: 3, as well as use of this sequence in a pharmaceutical composition. Applicants respectfully traverse this rejection.

Shimkets et al. disclose one sequence SEQ ID NO: 5309 that overlaps with certain residues within the sequence of SEQ ID NO: 3 of the instant invention. The patent application, however, is directed generally to identification of nucleic acids that contain nucleotide polymorphisms and their use in applications such as paternity analysis and genetic mapping. Nowhere does this patent application teach or suggest antisense targeted to the specific region of human phospholipase A2 group V of SEQ ID NO: 3 as now claimed. In order to anticipate a claim the reference cited must teach each and every limitation of the claim (MPEP 2131). Therefore, this reference cannot anticipate the claims as amended and withdrawal of this rejection is respectfully requested.

**III. Rejection of Claims Under 35 U.S.C. 103(a)**

Claims 1, 2 and 4-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Tischfield et al., in view of Balboa et al., Baracchini et al. (US Patent 5,801,154) and Taylor et al. (1999). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to make antisense sequences to target phospholipase A2 group V as taught by Tischfield et al. for inhibition of gene expression, as well as incorporating the modifications taught by Baracchini et al. The Examiner suggests one of skill would have been motivated by the teachings of Tischfield et al. because they expressly teach the sequence of the gene and because Balboa et al. teach antisense inhibition of the homologous mouse gene. The Examiner suggests a reasonable expectation of success is provided by Taylor in teaching that antisense can be made if a gene sequence is known. Applicants respectfully traverse this rejection.

As discussed *supra*, Applicants have amended the claims to recite that the antisense compounds of the instant invention are targeted to a specific region within the sequence of human phospholipase A2 group V (SEQ ID NO: 3). Also as discussed *supra*, Tischfield et al. fail to disclose antisense compounds targeted to

the specific region as claimed. As acknowledged by the Examiner, the other cited primary reference, Balboa et al. discloses only antisense to mouse phospholipase A2 group V, not antisense compounds of any type targeted to any region within the human gene as claimed. Accordingly these primary references, when combined, fail to teach or suggest the limitations of the claims as amended.

The secondary references cited, when combined with the primary references, fail to overcome the deficiencies in teaching of these primary references.

Taylor et al. (1999) disclose a method for systematically screening antisense compounds to understand gene function. Although this reference discusses how antisense compounds can be screened for activity, nowhere does this paper teach or suggest that antisense compounds targeted to a specific region within the sequence of human phospholipase A2 group V (SEQ ID NO: 3)can be used to successfully inhibit gene expression in cells as claimed.

Baracchini et al. (US Patent 5,801,154) disclose the use of antisense compounds to modulate expression of multi-drug resistance-associated protein. However, nowhere does this paper teach or suggest that antisense compounds targeted to a specific region within the sequence of human phospholipase A2 group V (SEQ

ID NO: 3)can be used to successfully inhibit gene expression in cells as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the art as combined fails to teach the limitations of the amended claims which recite antisense compounds targeted to a specific region within the sequence of human phospholipase A2 group V (SEQ ID NO: 3), a region that was not suggested by any of the cited references. Further, the combined art fails to provide one of skill with either the expectation of success or the motivation to combine the teachings. It is only with the specification in hand that one of skill would understand how to make and use compositions of the instant invention which are antisense compounds targeted to a very specific region within the sequence of SEQ ID NO: 3. MPEP 2143.01 states that the mere fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. There must some suggestion or motivation in the

reference to do so. Such suggestion or motivation is clearly lacking in the combination of references cited. Accordingly, withdrawal of this rejection is respectfully requested.

**IV. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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